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# **Long-term evaluation of pemphigus vulgaris: a retrospective consideration of 98 patients treated in an oral medicine unit in North-West Italy.**

Paolo G. Arduino<sup>1</sup>, Roberto Brocchetto<sup>1</sup>, Mario Carbone<sup>1</sup>, Alessio Gambino<sup>2</sup>, Veronica Sciannameo<sup>3</sup>, Davide Conrotto<sup>1</sup>, Marco Cabras<sup>1</sup>, Savino Sciascia<sup>4</sup>, Fulvio Ricceri<sup>3</sup>, Simone Baldovino<sup>4</sup>, Marco Carrozzo<sup>5</sup>.

<sup>1</sup>Department of Surgical Sciences, CIR-Dental School, University of Turin, Italy;

<sup>2</sup>Dimeas, Politecnico of Turin, Turin, Italy

<sup>3</sup>Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco, Italy;

<sup>4</sup>Center of Research of Immunopathology and Rare Diseases-Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley, Department of Clinical and Biological Sciences, University of Turin, Turin, Italy;

<sup>5</sup>Department of Oral Medicine, School of Dental Sciences, University of Newcastle upon Tyne, Newcastle upon Tyne, UK.

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Corresponding author:

Dr. Paolo G. Arduino

Department of Surgical Sciences, Oral Medicine Section

CIR-Dental School, University of Turin

Via Nizza 230, 10126 Turin, Italy. Tel: +390116331522.

E-mail: [paologiacomo.arduino@unito.it](mailto:paologiacomo.arduino@unito.it)

**Abstract**

**Background:** Despite the frequency of oral involvement, there are unexpectedly few studies of either on the oral manifestations of pemphigus or their long-term management, and diagnostic delay in Dentistry is frequent.

**Methods:** We have examined outcome of patients presenting with predominantly oral pemphigus vulgaris (PV). Ninety-eight subjects were followed-up for 85.12 months and treated with systemic steroids; 48 of them received adjunctive therapy with azathioprine, 16 with rituximab, 13 with mycophenolate mofetil, 3 with immunoglobulin, 1 with dapsone.

**Results:** Clinical remission was achieved in 80 patients (84.21%); 39 of them were off therapy and 41 on therapy. Fifteen patients were not in remission, having been under systemic therapy for 72.16 months. Sixty-nine patients developed detectable adverse effects. Two fatal outcomes were recorded. Each additional year of steroid therapy ensured 47% chance of developing 1 or 2 side effects, and 64% chance of developing more than 3 (ORs 1.47, CI 1.162-1.903; ORs 1.64, CI 1.107-2.130, respectively).

**Conclusion:** In one of the largest available cohort with the longest follow-up ever reported, we observed that the management remains need-based and patient-specific, still relying on systemic corticosteroids.

**Key words:** pemphigus vulgaris, oral manifestation, treatment and adverse effects.

## INTRODUCTION

Pemphigus is a group of potentially life-threatening and organ-specific autoimmune diseases, characterized by cutaneous and/or mucosal blistering.<sup>1-4</sup> Pemphigus can be mainly classified into 4 types: pemphigus vulgaris, pemphigus vegetans, pemphigus erythematosus and pemphigus foliaceus.<sup>5</sup> Pemphigus vulgaris (PV), the most common variant, is characterized by circulating IgG antibodies mainly directed against desmoglein 3 (Dsg3), with about half the patients also having Dsg1 autoantibodies.<sup>6-8</sup> Available epidemiological data suggest that PV affects 0.1-0.5 patients per 100.000 population per year.<sup>9</sup> The lesions of PV characteristically occur first in the oropharyngeal mucosa and later in the skin; other mucosae (e.g. oesophageal, genitalia and conjunctiva) may be involved as well.<sup>1</sup> The invariably fatal outcome of PV has changed dramatically since the 1950s, with the advent of corticosteroids.<sup>4,9</sup> However, there is a lack of consensus in the literature about the treatment of this disorder and this issue is further complicated by the fact that the therapy has to be individualized.<sup>10,11</sup>

Despite the frequency of oral involvement, there are unexpectedly few studies of either on the oral manifestations of pemphigus or their long-term management,<sup>9,12-16</sup> and diagnostic delay in Dentistry is frequent.<sup>17</sup>

The aim of this retrospective hospital-based study was to examine the different clinical features and treatment outcomes of Italian patients presenting with PV predominantly affecting the oral cavity.

## MATERIALS AND METHODS

### Study population

The case records of all new patients, admitted within the years 1993 to 2018, were reviewed. Medical and present complaint histories were acquired at the first consultation. The diagnosis was confirmed by histopathological examination with haematoxylin and eosin

staining, and direct immunofluorescence analysis. Assay of serum antibody titres by indirect immunofluorescence have been taken at the time of the first biopsy until 2004; later, the diagnosis was completed with the serum detection of antidesmosomal antibodies against desmoglein 1 (Dsg1) and/or desmoglein 3 (Dsg3).

## **Treatment**

Patients mainly received treatment with systemic corticosteroids (typical starting dose of 1-1.5 mg/kg per day of prednisone, for variable lengths of time usually of 2-4 months), alone or with azathioprine (at typical starting dose of 2 mg/kg per day), depending by clinical severity; corticosteroids were then tapered according to clinical activity. Topical therapy, using 0.05% clobetasol propionate ointment, was also added in many cases. Other systemic therapy used in minority cases were: rituximab (1000 mg on day 0 and 14), dapsone (50 mg/daily), mycophenolate mofetil (1.5-2 gr/day), and intravenous immunoglobulin therapy (4 monthly cycles at a dose of 2 g/kg per cycle). Rituximab and intravenous immunoglobulin therapy were provided at the Center of Research of Immunopathology and Rare Diseases (S. Giovanni Bosco Hospital, Turin, Italy). All patients on corticosteroid therapy were recommended to observe a diet low in salt, fat, and calories, and to increase the intake of potassium- and protein-rich meals in order to control weight gain, hyperglycaemia, and electrolyte imbalance.<sup>17</sup>

All patients had also a concomitant anti-fungal treatment against oropharyngeal candidosis, this consisting of miconazole gel applied once or twice daily, or nystatin (4 mL qid) or fluconazole rinses (5 mL bid). To prevent corticosteroid-induced osteoporosis,<sup>18</sup> some patients needed also to take sodium clodronate 100 mg/3.3 mL injection monthly, 1000 mg of calcium carbonate and 400 IU of Vitamin D daily<sup>19</sup> until 2011; later, the usual prescription was of alendronic acid (70 mg weekly) and 400 IU of Vitamin D daily.

We categorized the adverse effects as follow: 0 = patients who did not have any severe adverse reaction; 1 = patients who developed 1 or 2 severe adverse reactions; 2 = patients who developed 3 or more severe adverse reactions; 3 = dead patients.

### **Clinical data**

The oral mucosal disease severity (MDS) was assessed as mild (only localized to buccal mucosa), moderate (buccal and gingivolabial mucosal involvement), and severe (extensive oral mucosal involvement).<sup>9</sup> The involvement or not of skin and/or other mucosal membranes was documented as present or absent. All the patients had a complete ophthalmologic and dermatological examination; moreover, a flexible nasopharyngoscope was used to visualize the nasal mucosa, epiglottis, pharynx, larynx and proximal oesophagus.

In a theoretical manner, we also subdivided patients based on the date of the initial diagnosis [0 = patients diagnosed until 2006; 1 = patients diagnosed since 2007], trying to assess whether the increased clinical skills acquired over the years could in some way influence therapeutic results. Therapeutic response was assessed by clinical improvement, in term of remission of existing lesions. Control of disease activity was defined as ‘the time at which new lesions cease to form and established lesions begin to heal’ in accordance with international consensus statement on end points and therapeutic response for PV. Outcome measures were defined as follows: complete remission off therapy (absence of new or established lesions while the patient is off all systemic therapy for at least 2 months); complete remission on therapy (absence of new lesions or established lesions while the patients is receiving minimal therapy, e.g.  $\leq 10$  mg/d prednisone or equivalent and/or minimal adjuvant therapy for at least 2 months); partial remission on therapy (defined as the presence of transient new lesions that heal within one week while the patient is receiving minimal therapy, including topical steroids).<sup>20</sup>

Methods were conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and statement.<sup>21</sup>

The ethics review board of the CIR - Dental School approved the study (CIR-PO 2018/2435).

### **Statistical analysis**

The non-normality of the distribution of continuous variables were checked via Kolmogorov-Smirnov tests, so Kruskal-Wallis tests were performed to evaluate the differences between continuous variables. Chi squared or Fisher's exact tests when appropriate were computed to evaluate the differences between qualitative variables. The Spearman's rank correlation coefficient was computed to evaluate the correlation between the delay in diagnosis and the mucosal severity involvement at baseline. Odds ratios (ORs) and 95% confidence intervals (95% CI) were computed by means of multivariable logistic regression models, in order to test the effect of the length of the steroid therapy on the side effects. Models were adjusted by sex, date of diagnosis (before 2007 or after) and age at diagnosis. Hypothesis tests were 2-sided and statistical significance was set at  $\alpha=0.05$ . All statistical analyses were performed using SAS V9.3 (SAS Institute Inc., NC27513-2414, USA).

## **RESULTS**

### **Demographic features**

The study group comprised 95 unrelated Caucasian patients (60 female and 35 male), together with 2 female and 1 Afro-Caribbean male (F : M; 1.65 : 1), mean age 54.56 ( $\pm 14.95$ ). The majority of the patients (24, 24.49%) was in the 6<sup>th</sup> decade of life.

### **Oral disease profile and mucosal or cutaneous involvement**

The duration of oral symptoms before definitive diagnosis varied from 1 to 36 months, leading to an average delay of 24 weeks (mean times of 23.42 weeks for male and 20.20



weeks for female). The delay of diagnosis was however not statistically associated with the degree of oral involvement ( $\rho = 0.13$ ;  $P = 0.20$ ).

By definition, all patients had oral lesions at presentation. Considering the MDS index, it was mild in 20 cases (20.41%), moderate in 48 (48.98%) and severe in 30 cases (30.61%). Patients diagnosed since 2007 statistically had a worse oral involvement ( $p = 0.01$ ) (Table 1). The buccal mucosae were the single most common site (32.93%), followed by the palate (22.76%), tongue plus floor of the mouth (18.29%), gingiva (17.48%), and lips (8.54%). Eleven patients (11.22%) had only gingival lesion at the time of presentation. Soreness was the most commonly reported oral symptom in almost all patients, while only 30 (30.61%) of them described the pain as being notably severe.

Forty-three patients (43.87%) had other mucosal involvement, being the pharynx clinically affected in 33 cases, nasal mucosa in 11, vagina in 4, larynx in 10 and oesophagus in 3; 2 patients had also the involvement of anal mucosa. Conjunctiva was affected in 4 patients. Forty-one patients (41.83%) presented with cutaneous manifestation, of whom 6 developed cutaneous blisters after starting systemic treatment during the follow-up time. Skin involvement was statistically more evident in patients diagnosed since 2007 ( $p = 0.04$ ).

### **Associated diseases**

The medical histories included essential hypertension (22 patients), osteoporosis (7 patients) and one patient each had hepatitis C infection, cardiomyopathy, psoriasis, depression, hypothyroidism, ulcerative rectocolitis, allergic rhinitis, prostatic adenoma and colon cancer. All those patients with pre-existing associated diseases were treated after consultation with relevant medical specialists. Medical histories of 54 patients were unremarkable.

### **Treatment provided**

Ninety-five patients were treated initially with systemic corticosteroids *per os*. During this treatment time [lasting on average 48 months ( $\pm 49.59$ )], 81 patients received corticosteroid-sparing adjunctive therapy as it follows: 48 with azathioprine, 16 with intravenous rituximab, 13 with mycophenolate mofetil, 3 with intravenous immunoglobulin therapy and 1 with dapsone. The use of azathioprine statistically decreased since 2007 in a statistical manner, differently from the use of rituximab which increased but not statistically (Table 1).

Three patients (with very mild lesions) controlled their disease only by using topical corticosteroids; 63 patients, together with the systemic therapy, used topical clobetasol mainly to control oral limited soreness, or restricted skin and nasal lesions.

We gradually tapered the corticosteroid down, for patients in remission (starting after having reached at least the 75% of oral lesion remission), until we reached a maintenance dose of 5-20 mg daily. If the lesions did not relapse, the corticosteroid was again tapered until a maintenance dose of 2.5 mg every two, three or four days, and then stopped.

### **Treatment outcome**

Eighty-six of the 98 patients were still being followed at the Oral Medicine Unit when this study was performed. Patients were followed-up for 85.12 months on average ( $\pm 59.35$ ) with a recorded median of 73.50 months (Table 2).

The average time to achieve complete clinical remission was  $3.9 \pm 2.72$  months after commencement of therapy. In 39 (41.05%) of the 95 patients who received systemic treatment there was the complete resolution of disease in less than 6 months, and at the end of the follow-up period they were not under treatment; they remained under steroid therapy for 53.15 months ( $\pm 38.89$ ). Forty-one (43.15) patients were disease free but still taking immunosuppressive therapy but tapering it down, for 61.51 months ( $\pm 51.93$ ). Fifteen (15.8%) patients did not respond, having been under systemic therapy for 72.16 months ( $\pm 63.51$ ).

Females tended to have a higher percentage of unresponsive lesions than males (22.95% vs 10.81%) ( $p = 0.0305$ ).

The use of azathioprine seemed not to be related to a better percentage of possible improvement with the 25% of total treated cases who cannot tolerate it (Table 1). Such conclusion cannot be drawn for the other immunosuppressive agents, as their limited use did not allow the same kind of analysis.

Patients who presented with joint skin or mucosal involvement had higher unresponsive rates compared to patients with exclusive oral involvement ( $P = 0.0481$ ,  $P = 0.0379$ , respectively). Similarly, patients with greater oral involvement had worse rates of complete response ( $P = 0.0337$ ). Differently, no differences were reported if considering the oral site of involvement ( $P = 0.6506$ ).

Differently, age at baseline and diagnostic delay did not seem to influence the outcome of the therapy in terms of oral lesions remission.

Patients diagnosed since 2007 had the similar chance of being under remission if compared to those diagnosed before ( $p = 0.89$ ), but they were treated with corticosteroids for a shorter period ( $p = 0.01$ ).

### **Adverse effects**

Weight gain and cushinoid features were observed almost in every patient who took 1.5 mg/kg/day of systemic prednisone, after approximately 1-3 months of treatment. These changes were however reversible after the decrease of the induction dose.

Sixty-nine patients (72.63%) on systemic treatment developed detectable adverse effects from the immunosuppressive drugs. Among these, 54 patients developed less than 2 adverse effects while 15 patients manifested 3 or more. It was possible to report 15 cases of hypertension (plus 6 cases of other cardiovascular problems), 11 cases of hyperglycaemia, 23 cases of osteoporosis, 9 cases of gastric diseases, 10 cases of mood

disorders, 3 cases of cataract and 2 cases of pneumonia. Other unusual effects, reported only once, were detailed as follow: walking problems, hair loss, folliculitis, tremor, hypokalaemia, and erythroderma. One patient had a myocardial infarction after 5 weeks of therapy with steroids alone and a femoral fracture after 20 weeks.

Two fatal outcomes, likely linked to the therapy, were recorded over the follow-up period (2.10% of patients who underwent systemic management; 2.04% of the total study population).

Table 3 described the effect of the length of the steroid therapy (LST) on the side effects (also adjusted by sex, date of diagnosis and age at the time of first diagnosis). It was possible to state that each additional year of steroid therapy ensures 47% chance of developing 1 or 2 side effects, and 63% chance of developing more than 3 side effects (ORs 1.487 CI 1.162-1.903; ORs 1.536 CI 1.107-2.130, respectively).

## DISCUSSION

There have been few studies describing the oral manifestations and treatment outcomes in PV. However, it is thought that in most cases, the oral lesions are the first manifestation of the disease<sup>13,14,22</sup> and a significant proportion of PV patients can just have oral lesions.<sup>12-16</sup> In all our cases the oral lesions were the first manifestation of the disease, in the form of blisters and/or ulcers, sometimes associated with skin disease or other mucosal membranes involvement. The most commonly affected sites in the present study were the buccal mucosae and the gingival, in accordance with recent findings.<sup>23-25</sup>

PV affects all races and both sexes, and is more frequent in middle aged and elderly patients,<sup>3</sup> with a peak incidence between the fifth and sixth decades of life. In this report, we described 98 patients with PV, with a preponderance of female, and about two third of them were in the 4<sup>th</sup> to 6<sup>th</sup> decade of their life. The youngest patient in this report was an 18-year-old female and the oldest being an 85-year-old woman.

Intra oral involvement usually precedes the development of extraoral disease.<sup>3,8</sup> In our cohort, many patients were at first misdiagnosed, frequently as having aphthous or herpetic stomatitis or candidosis, and erroneously treated for a long period. Male patients tended to have symptoms for longer periods before receiving a definitive diagnosis than females (mean times of 23.42 weeks for male and 20.20 weeks for female), and this is similar to previous findings.<sup>13</sup>

The early diagnosis of PV has been suggested to be fundamental to achieve a long-term remission with minimal adverse-effects and healthier prognosis.<sup>23, 24</sup> Nonetheless, in our series, diagnostic delay did not seem to be statistically related to faster improvement, neither in terms of duration of the corticosteroid therapy nor in absolute terms of disappearance of oral signs and symptoms. This could possibly be explained because previously reported diagnostic delays in PV were possibly greater than in our cohort but also because often in published studies there was no clear distinction between cutaneous and oral involvement. Indeed, in our series skin involvement was correlated with a worse prognosis. Moreover, female patients tended to have a statistically worse prognosis if compared to males; this type of information has never been documented in an oral clinical setting.

Cases of oral PV usually responded very well to the corticosteroid therapy, and in our study the average time for a complete clinical remission was quite similar to that reported by others in similar clinical setting,<sup>16</sup> commonly less than six months.

Ideally, the management of PV aims to induce and maintain clinical remission with minimum adverse effects. Because of the lack of international agreed recommendations, either the dosage of corticosteroids and choice of adjuvant agents usually reflect the experience of clinicians at various centres.<sup>23,26</sup>

A review of 77 studies, reported a mortality rates of 70.5% before the advent of systemic corticosteroids, 21.4% when steroids were used, and 3.7% when steroids were pooled with adjuvant drugs, and the latter is similar to our results.<sup>27</sup>

At the end of 2012, an interim analysis of collected data showed that azathioprine was poorly effective in achieving disease control if used together with corticosteroids, with many patients unable to tolerate it, similarly to what has been recently reported in cases of mucosal-predominant PV.<sup>28</sup> Since then we decided to stop prescribing azathioprine as steroid sparing partner. This seems quite in contradiction with very recent findings from a retrospective study from Japan, suggesting that azathioprine monotherapy could be a viable treatment option for mild PV.<sup>29</sup> However, this study enrolled just 5 patients and the exact oral involvement was not reported.

One particular strength of our report is the duration of the follow-up. Patients have been followed up from 6 months to 20 years and 57 patients have been followed for more than 5 years. This considerable period allowed us to show that shorter corticosteroid therapies produced less adverse reactions but similar results in terms of complete oral remission compared to longer ones. Moreover, whereas age at baseline or diagnostic delay did not seem to influence the outcome of the treatment, patients with skin and mucosal involvement or with greater oral involvement had lower remission rate and needed longer corticosteroid therapy.<sup>28</sup>

We would also emphasize that our findings suggest that the increased experience of the clinicians in treating PV could have led to a statistically significant shorter period of corticosteroid therapy. However, this could have also been influenced by the increase use of rituximab as a second line treatment. Notably, it has recently been reported that first-line use of rituximab plus short-term prednisone for patients with PV/pemphigus foliaceus is more effective than prednisone alone, and has fewer adverse events.<sup>29</sup> Further researches in oral PV should be likely directed towards the use of rituximab as first therapeutic option, to assess whether this treatment modality allows a faster resolution of the mucosal lesions, and can reduce the duration of corticosteroids' use.<sup>30</sup>

## **CONCLUSION**

This is one of the largest groups of oral PV patients with such long follow up ever reported. We confirm that the disease can be effectively controlled and followed up also in an oral medicine unit with remission rates similar to dermatological cohorts. According to our findings, systemic corticosteroid should be still considered, at least for predominant oral manifestations, the medication of choice.

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**Conflicts of interest**

None declared.



## REFERENCES

1. Mimouni D, Anhalt GJ. Pemphigus. *Dermatologic Therapy*. 2002;15:362-368.
2. Bystryn JC, Rudolph JL. Pemphigus. *Lancet*. 2005;366:61-73.
3. Black M, Mignona MD, Scully C. Number II. Pemphigus vulgaris. *Oral Dis*. 2005;11:119-130.
4. Cirillo N, Cozzani E, Carrozzo M, Grando SA. Urban legends: pemphigus vulgaris. *Oral Dis*. 2012;18:442-458.
5. Nishikawa T, Hashimoto T, Shimizu H, Ebihara T, Amagai M. Pemphigus: from immunofluorescence to molecular biology. *J Dermatol Sci*. 1996;12:1-9.
6. Ahmed AR, Carrozzo M, Caux F, et al. Monopathogenic vs multipathogenic explanations of pemphigus pathophysiology. *Exp Dermatol*. 2016;25:839-846.
7. Hashimoto T. Recent advances in the study of the pathophysiology of pemphigus. *Arch Dermatol Res*. 2003;295:S2–11.
8. Becker BA, Gaspari AA. Pemphigus vulgaris and vegetans. *Dermatol Clin*. 1993;11:429-452.
9. Mahajan VK, Sharma NL, Sharma RC, Garg G. Twelve-year clinico-therapeutic experience in pemphigus: a retrospective study of 54 cases. *Int J Dermatol*. 2005;44:821-827.
10. McMillan R, Taylor J, Shephard M, et al. World Workshop on Oral Medicine VI: a systematic review of the treatment of mucocutaneous pemphigus vulgaris. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;120:132-142.
11. Martin LK, Werth V, Villanueva E, Segall J, Murrell DF Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev*. 2009;(1):CD006263.
12. Laskaris G, Sklavounou A, Stratigos J. Bullous pemphigoid, cicatricial pemphigoid

- and pemphigus vulgaris. A comparative clinical survey of 278 cases. *Oral Surg Oral Med Oral Pathol*. 1982;54:656-662.
13. Robinson JC, Lozada-Nur F, Frieden I. Oral pemphigus vulgaris: a review of the literature and a report on the management of 12 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;84:349-355.
  14. Scully C, Paes De Almeida O, Porter SR, Gilkes JJ. Pemphigus vulgaris: the manifestations and long-term management of 55 patients with oral lesions. *Br J Dermatol*. 1999;140:84-89.
  15. Camacho-Alonso F, Lopez-Jornet P, Bermejo-Fenoll A. Pemphigus vulgaris. A presentation of 14 cases and review of the literature. *Med Oral Patol Oral Cir Bucal*. 2005;10:282-288.
  16. Mignogna MD, Fortuna G, Leuci S, Ruoppo E. Oropharyngeal pemphigus vulgaris and clinical remission: a long-term, longitudinal study. *Am J Clin Dermatol*. 2010;11:137-145.
  17. Sirois DA, Fatahzadeh M, Roth R, Ettlin D. Diagnostic patterns and delays in pemphigus vulgaris: experience with 99 patients. *Arch Dermatol*. 2000;136:1569-1570.
  18. Rencic A, Caeiro JP, Hernandez MI, Nousari HC. Prophylaxis in dermatologic patients receiving immunosuppressive therapy. *Dermatologic Ther*. 2002;15:352-361.
  19. Frediani B, Falsetti P, Baldi F, Acciai C, Filippou G, Marcolongo R. Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. *Bone*. 2003;33:575-581.

20. Murrell DF, Dick S, Ahmed AR, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol.* 2008;58:1043-1046.
21. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;61:344–349.
22. Korman N. Pemphigus. *J Am Acad Dermatol.* 1988;18:1219-1238.
23. Ljubojevic S, Lipozencic J, Brenner S, Budimcic D. Pemphigus vulgaris: a review of treatment over a 19-year period. *JEADV* 2002; 16: 599-603.
24. Kumar S, De D, Handa S, et al. Identification of factor associated with treatment refractoriness of oral lesions in pemphigus vulgaris. *Br J Dermatol.* 2017;177:1583-1589.
25. Svecova D. Pemphigus vulgaris: a clinical study of 44 cases over a 20-year period. *Int J Dermatol.* 2015;54:1138-1144.
26. Iamaroon A, Boonyawong P, Klanrit P, Prasongtunskul S, Thongprasom. Characterization of oral pemphigus vulgaris in Thai patients. *J Oral Science.* 2006;48:43-46.
27. Carson PJ, Hameed A, Ahmed AR. Influence of treatment on the clinical course of pemphigus vulgaris. *J Am Acad Dermatol.* 1996;34:645-652.
28. Ojaimi S, O'Connor K, Lin MW, Schifter M, Fulcher DA. Treatment outcomes in a cohort of patients with mucosal-predominant pemphigus vulgaris. *Intern Med J.* 2015;45:284-292.
29. Kakuta R, Yamagami J, Funakoshi T, Takahashi H, Ohyama M, Amagai M. Azathioprine monotherapy in autoimmune blistering diseases: A feasible option for mild to moderate cases. *J Dermatol.* 2018;45:334-339.

30. Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomized trial. *Lancet*. 2017;389:20131-2040.